

Letter

Probability curves focusing on symptom severity during an oral food challenge

A diagnosis of food allergy is definitively made by ingesting the food in question during an oral food challenge (OFC). Because OFCs sometimes result in severe allergic reactions, including anaphylaxis, antecedent examinations, such as measuring serum specific IgE levels, are necessary to avoid the risks of OFCs. Probability curves that can predict a positive OFC result according to a specific IgE level have been reported to be a useful guide before an OFC is performed¹ and can be affected by factors such as patient's age,² objective of the OFC,³ and an antigen for specific IgE.^{3,4} However, no previous reports have focused on induced symptom severity in OFCs.⁵ In the present study, we report probability curves that predict the severity of induced symptoms on the basis of ovomucoid (OVM) specific IgE levels.

In the present study, between October 2012 and July 2013, Japanese children aged 0 to 6 years who were examined for OVM specific IgE and subsequently underwent a boiled-egg OFC at our pediatric clinics or hospitals were included. The 11 institutes that participated in this study essentially used the following OFC protocol: 1, 2, 4, 8, and 16 g of hen's egg white were boiled for at least 20 minutes and consumed at 15- to 30-minute intervals. The indication for OFC was decided according to the Japanese Pediatric Guideline for Food Allergy 2012⁶ on the basis of clinical history of food allergy and related specific IgE levels. Patients with highly predicting positive OFC results by established positive predictive values^{1–4} or anaphylactic history within a year did not undergo OFC. We assessed the severity of the induced symptoms with the grading system of the guideline based on Sampson's anaphylaxis severity score⁷ (eTable 1) and prospectively recorded the results on the same database system. Mild objective symptoms, such as a small localized rash, or ambiguous subjective symptoms, such as abdominal pain, were temporarily considered indecisive. Symptoms were carefully assessed with subsequent doses during the challenge or after symptom recurrence during the home diet; however, they remained indecisive in some cases. We considered the OFC result negative when 30 g or more of total boiled egg white was consumed without any symptoms in children 3 years or older or when younger children consumed 15 g or more of the boiled egg white. Other patients with no allergic symptoms who could not consume the sufficient dose were excluded from this study. OVM specific IgE antibodies were measured by the ImmunoCAP test (Phadia AB, Uppsala, Sweden) within 3 months before the OFC. In the statistical analysis, the measurements were considered to be 0.17 kU_A/L if the level was less than 0.35 kU_A/L and 100 kU_A/L if the level was 100 kU_A/L or higher. The present study was approved by the Local Research Ethics Committee and was conducted according to the Declaration of Helsinki principles.

We used logistic regression analysis to assess the association between OVM specific IgE and the OFC outcome. The OFC outcomes

in this study were analyzed for symptom severity greater than grades 1, 2, or 3. Indecisive cases were considered equivalent to grade 1 for safety purposes. Probability curves were drawn on the basis of the results of the logistic regression analysis. Statistical analysis was performed using JMP statistical software, version 8.0.2 (SAS Institute Inc, Cary, North Carolina).

In our study population ($n = 156$, eTable 2), 81 patients (52.6%) had active eczema, 16 (10.6%) were taking medications for asthma, and 10 (6.4%) had a history of anaphylaxis after consuming hen's eggs. The 50 children (32.1%) in our study consumed hen's egg for the first time during this OFC. The median value of OVM specific IgE levels was 2.03 kU_A/L (interquartile range, 0.41–5.57 kU_A/L). In the OFC, induced symptoms (eTable 3) greater than grades 1, 2, and 3 were seen in 75 children (48.1%), 42 children (27.0%), and 10 children (6.4%), respectively. On the basis of the severity of the induced symptoms in the same population, we drew 3 different probability curves that predicted the results of the OFC according to the OVM specific IgE levels (Fig 1). The OVM specific IgE level with a 95% probability of predicting any symptoms was 22.4 kU_A/L and that with a 5% probability of predicting symptoms greater than grade 3 was 3.8 kU_A/L (eTable 4). Subsequent analysis for children aged 0 to 2 years ($n = 118$, eTable 2) revealed a highly predictive value for severe induced symptoms (eFig 1). The level with a 95% positive predictive value (PPV) for symptoms greater than grade 1 was 24.2 kU_A/L and that with a 5% PPV for symptoms greater than grade 3 was 4.2 kU_A/L (eTable 4).

The present study has 2 novel advantages. First, to the best of our knowledge, this is the first study to show probability curves

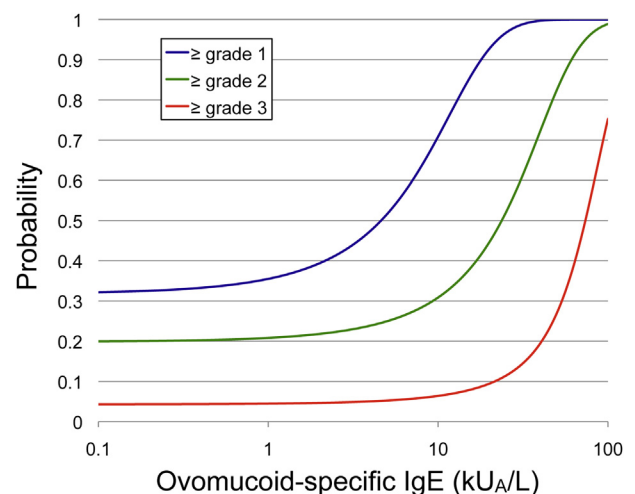


Figure 1. Probability curves for ovomucoid specific IgE levels in patients aged 0 to 6 years ($n = 156$). The fitted predictive probability curves predicting the outcomes of a boiled-egg food challenge are shown.

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that focus on the induced symptom severity during OFC. In clinical practice, it is important to predict a positive OFC result and the induced symptom severity. If the predictive outcome is more severe, more caution should be taken during OFC. We considered a 5% PPV for induced symptoms greater than grade 3 as a useful indicator for performing OFC in a less intensive setting, such as a clinic or outpatient hospital department. Second, the present study was conducted at multiple institutions where patients could visit regarding their suspected food allergy and then undergo a subsequent OFC. Most studies that reported the usefulness of probability curves in OFC took place at a single clinical center specialized for food allergy^{1–4}; therefore, our study population is more appropriate for avoiding inclusion biases. Because the PPV of OFC varies, depending on the study population,⁸ a probability curve from a similar population should be used in each clinical setting. The probability curve that focuses on the severity of induced symptoms is a new tool to decide indications for OFC and will contribute to a safer clinical practice of food allergy testing.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.04.001>.

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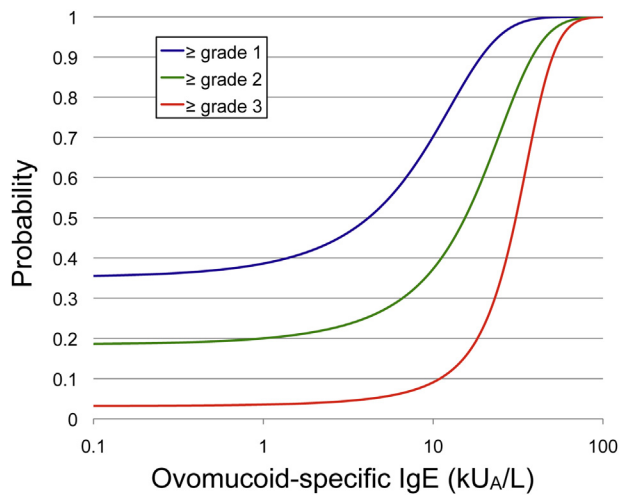
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References

- [1] Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107:891–896.
- [2] Komata T, Soderstrom L, Borres MP, et al. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol*. 2007;119:1272–1274.
- [3] Haneda Y, Kando N, Yasui M, et al. Ovomucoids IgE is a better marker than egg white-specific IgE to diagnose boiled egg allergy. *J Allergy Clin Immunol*. 2012;129:1681–1682.
- [4] Ando H, Movérare R, Kondo Y, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol*. 2008;122:583–588.
- [5] Sicherer SH, Wood RA. American Academy of Pediatrics Section On Allergy And Immunology. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics*. 2011;129:193–197.
- [6] Japanese Society of Pediatric Allergy and Clinical Immunology. *Japanese Pediatric Guideline for Food Allergy 2012* [in Japanese]. Tokyo, Japan: Kyowa Kikaku; 2011.
- [7] Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111:1601–1608.
- [8] Peters RL, Allen KJ, Dharmage SC, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol*. 2013;132:874–880.

**eTable 2**

Population characteristics

Characteristic	0–6 Years Old	0–2 Years Old
No. of patients	156	118
Age, median (quartile), y	1 (1–2)	1 (1–2)
Male sex, No. (%)	111/156 (71.2)	81/118 (68.6)
History, No. (%)		
Active eczema ^a	81/154 (52.6)	60/116 (51.7)
Active asthma ^a	16/151 (10.6)	8/116 (6.9)
Anaphylactic history of hen's egg	10/156 (6.4)	5/118 (4.2)
No history of consumption of hen's egg	50/156 (32.1)	43/118 (36.4)
Laboratory data, median (quartile)		
Egg white specific IgE, kUA/L	6.52 (2.60–16.5)	6.33 (2.51–15.5)
Ovomucoid specific IgE, kUA/L	2.03 (0.41–5.57)	1.62 (0.17–4.75)
Outcome of oral food challenge, No. (%)		
Negative	81/156 (51.9)	61/118 (51.7)
Indecisive	4/156 (2.6)	4/118 (3.4)
Grade 1	29/156 (18.6)	21/118 (17.8)
Grade 2	32/156 (20.5)	23/118 (19.5)
Grade 3	5/156 (3.2)	5/118 (4.2)
Grade 4	5/156 (3.2)	4/118 (3.4)
Grade 5	0/156	0/118

^aMissing values.**eTable 1**

Grading of symptoms observed during oral food challenge

Grade	Skin	Gastrointestinal tract	Respiratory tract	Cardiovascular	Neurologic
1	Localized pruritus, flushing, urticaria, angioedema	Oral discomfort, pruritus, lip swelling	Pharyngeal discomfort, pruritus		
2	Generalized pruritus, flushing, urticaria, angioedema	Nausea, vomiting or diarrhea (1–2), transient colic	Mild congestion, rhinorrhea, transient sneeze/cough		Change in activity level
3	Any of the above	Vomiting or diarrhea (≥3), persistent colic	Marked congestion, rhinorrhea, persistent sneeze/cough, laryngeal pruritus	Tachycardia (increase >15 beats/min)	Anxiety
4	Any of the above	Any of the above	Laryngeal tightness, hoarseness, “barky” cough, difficulty swallowing, dyspnea wheezing, cyanosis	Dysrhythmia and/or mild hypotension	“Light headedness,” feeling of “impending doom”
5	Any of the above	Any of the above	Respiratory arrest	Severe bradycardia and/or hypotension or cardiac arrest	Loss of consciousness

eTable 3

Induced symptoms in OFC

Symptoms	No. (%) of Positive OFC Results
Any	75
Skin	70 (93.3)
Gastrointestinal tract	20 (26.7)
Respiratory tract	16 (21.3)
Cardiovascular	1 (1.3)
Neurologic	3 (3.0)
Anaphylaxis	11 (14.7)

Abbreviation: OFC, oral food challenge.

eTable 4

Diagnostic abilities of ovomucoid specific IgEs for boiled-egg challenge outcomes

Outcomes	0–6 Years Old		0–2 Years Old	
	Grade 1 or Higher	Grade 3 or Higher	Grade 1 or Higher	Grade 3 or Higher
Cutoff, kU _A /L	22.4	3.8	24.2	4.2
Sensitivity, %	14.7	80.0	8.8	77.8
Specificity, %	100	70.5	100	77.1
Positive predictive value, %	100	15.7	100	21.9
Negative predictive value, %	55.9	98.1	54.0	97.7